REMARKS/ARGUMENTS

Withdrawn Rejections

Applicants wish to thank the Examiner for withdrawal of the objections and rejection outlined in the instant Office Action on pages 2-3.

Claim Rejections

Rejections under 35 U.S.C. § 103

The Examiner has rejected pending claims 1-2, 5-6 and 9-10 as allegedly being unpatentable over Ghirri et al. (US6352974) in view of Bay et al. (US20020065255). The Examiner alleges that Ghirri provides all the elements of the pending claims but concedes that "Ghirri does not teach an oral calcitionin pharmaceutical composition comprising a delivery agent selected from the group consisting of 5-CNAC, SNAD, SNAC, and said delivery agent is disodium salt thereof." (Office Action at p. 6). However, the Examiner alleges that Bay teaches "pharmaceutical compositions comprising a delivery agent, which is a disodium salt of 5-CNAC, SNAD, or SNAC, and an active agent, such as salmon calcitonin." (*Id.*). The Examiner concludes that it would have been obvious to combine the teachings of Ghirri with those of Bay, because Bay teaches that the disodium salt of 5-CNAC, SNAD, or SNAC can increase efficacy for delivering the active agent, and consequently, one of ordinary skill would have a reasonable expectation of successfully delivering the salmon calcitonin for therapeutic treatment. (*Id.* at pp. 6-7). For the following reasons, that rejection is respectfully traversed.

I. Obviousness Standards

Graham v. John Deere Co. of Kansas City, 383 U. S. 1, 17-18 (1966), establishes an objective analysis for applying §103 to a question of obviousness: "the scope and content of the prior art are . . . determined; differences between the prior art and the claims at issue are . . . ascertained; and the level of ordinary skill in the pertinent art resolved." The United States Patent and Trademark Office bears the burden of establishing a prima facie case of obviousness based on the results of the factual inquiries under *Graham*. The *prima facie* case generally requires three showings: 1) some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or combine reference teachings; 2) a reasonable expectation of success; and 3) that the prior art reference or combination of references teaches or suggests all the claim limitations. MPEP §2143.

The United States Patent and Trademark Office bears the burden of establishing a *prima facie* case of obviousness based on the results of the factual inquiries under *Graham*. The *prima facie* case requires three showings:

1) some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or combine reference teachings;

2) a reasonable expectation of success; and

3) that the prior art reference or combination of references teaches or suggests all the claim limitations.

In the present application, the results of the factual inquiries under *Graham* do not support a *prima facie* case that the pending claims are obvious under 35 U.S.C. §103(a).

II. Failure to Support a *Prima Facie* Case

a. The Combination of Ghirri and Bay Neither Discloses Nor Suggests All Elements of Applicants' Claims

All claims currently require "between 0.4 and 2.5 mg of salmon calcitonin in free or salt form." The Office alleges that this dosage element may be found in Ghirri. (Office Action at p. 6). The Office is mistaken. At column 3, Ghirri teaches that salmon calcitonins typically have an activity of up to 6,500 IU/mg. Indeed, Example 1 at column 8 of Ghirri uses salmon calcitonin with a potency of 6,567.7 IU/mg. Ghirri indicates at column 6 that the pharmaceutical preparations therein preferably have a unit dose of active material from about 20 – 600 I.U. Given the salmon calcitonin activity of 6,500 IU/mg recited in column 3 of Ghirri, a Ghirri composition would contain about 3 μg – 92 μg of salmon calcitonin. This is also reflected in the Ghirri composition of Examples 4 and 5 (having 105 I.U. of salmon calcitonin, which is about 15 μg of salmon calcitonin), Examples 6-7 and 10 (having 400 I.U. of salmon calcitonin, which is about 61 μg of salmon calcitonin) and Example 9 (having 200 I.U. of salmon calcitonin, which is about 30.5 μg of salmon calcitonin).

This failure of Ghirri to disclose the claim element "between 0.4 and 2.5 mg of salmon calcitonin in free or salt form" is not supplemented by the disclosure of Bay, because Bay uses doses of 25-4000 mg/kg of salmon calcitonin for administration to rats and monkeys. (See, e.g., Example 4 and Tables 6 and 10 of Bay). Accordingly, Ghirri teaches far less of a salmon calcitonin dose than is used by Applicants, while Bay teaches far more of a salmon calcitonin dose than is used by Applicants.

The aforementioned element of Applicants' claims cannot reasonably be said to be present in the asserted combination of references. The failure of an asserted combination to teach or suggest each and every feature of a claim remains fatal to an obviousness rejection under 35 U.S.C. § 103, despite any recent revision to the Manual of Patent Examining Procedure (MPEP). Section 2143.03 of the MPEP requires the "consideration" of every claim feature in an obviousness determination. To render the instant independent claims unpatentable, however, the Office must do more than merely "consider" each and every feature for this claim. Instead, the asserted combination must also teach or suggest each and every claim feature. *See In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974) (emphasis added) (to establish *prima facie* obviousness of a claimed invention, all the claim features must be taught or suggested by the prior art). Indeed, as the Board of Patent Appeal and Interferences has recently confirmed that a proper obviousness determination requires that the Office make "a searching comparison of the claimed invention - *including all its limitations* - with the teaching of the prior art." *See In re Wada and Murphy*, Appeal 2007-3733, *citing In re Ochiai*, 71 F.3d 1565, 1572 (Fed. Cir. 1995) (emphasis in original). Further, the necessary presence of all claim features is axiomatic, since the Supreme Court has long held that obviousness is a question of law based on underlying factual inquiries, including ascertaining the differences between the claimed invention and the prior art. *Graham*, 383 U.S. 1 (1966). Applicants submit that this is why Section 904 of the MPEP instructs examiners to conduct an art search that covers "the invention as *described and claimed*." (emphasis added). Lastly, Applicant respectfully directs attention to MPEP § 2143, the instructions of which buttress the conclusion that obviousness requires at least a suggestion of all of the features of a claim, since the Supreme Court in *KSR Int'l v. Teleflex Inc.* stated that "there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *KSR Int'l v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007) (*quoting In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006).

In sum, it remains well-settled law that obviousness requires at least a suggestion of all of the features in a claim. *See In re Wada and Murphy*, *citing CFMT, Inc. v. Yieldup Intern. Corp.*, 349 F.3d 1333, 1342 (Fed. Cir. 2003) (stating "obviousness requires a suggestion of all limitations in a claim.") and *In re Royka*, 490 F.2d 981, 985 (CCPA 1974)). Based on the evidence as a whole, the combination of references cited by the Office does not support a finding of *prima facie* obvious. *See* MPEP § 2144.08; *In re Bell*, 991 F.2d 781,784 (Fed. Cir. 1993); *In re Kulling*, 897 F.2d 1147, 1149 (Fed. Cir. 1990)). The Office has not shown a suggestion or motivation to modify the citations or combine the citations teachings to arrive at Applicants' claims. In the present application, the results of the factual inquiries under *Graham v. John Deere Co. of Kansas City*, 383 U. S. 1, 17-18 (1966) do not support that the pending claims are *prima facie* obvious under 35 U.S.C. §103(a).

In addition, the Office is required to consider what the prior art as a whole teaches. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984) (stating that a prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention). The MPEP specifically requires the Office to "consider[] both the invention and the prior art references as a whole" and warns of distilling an invention down to a "gist" or "thrust", as such distillation disregards the "as a whole" requirement for an obviousness analysis. *See W.L. Gore*, 721 F.2d 1540 (Fed. Cir. 1983); MPEP § 2141.02. Bay provides a very large dose of 800 mg salmon calcitonin to monkeys (Example 4) and 25 mg/kg – 4000 mg/kg salmon calcitonin to rats in order to use, e.g., 5-CNAC to achieve the salmon calcitonin serum concentrations shown in Bay's Examples. Therefore, as a whole, Bay suggests that a large dose of salmon calcitonin would be required in combination with, e.g., 5-CNAC to achieve high levels of salmon calcitonin *in vivo*. Yet, Applicants methods require *only* between 0.4 and 2.5 mg of salmon calcitonin in free or salt form. Accordingly, taken as a whole, Bay teaches away from using the doses recited in Applicant's claimed methods.

b. The Combination of Ghirri and Bay Does Not Provide a Reasonable Expectation of Success at Arriving at Applicants' Claims

A *prima facie* case of obviousness must also establish that there is a reasonable expectation of success at arriving at Applicants' claimed subject matter upon combining Ghirri and Bay. *In re O'Farrell*, 853 F.2d 894, 903-04 (Fed. Cir. 1988). However, in the instant situation, the asserted combination of Ghirri and Bay does not provide a reasonable expectation of success at arriving at Applicants' claims.

First, it must be understood that oral delivery of proteins is extremely difficult to achieve, and hence extremely unpredictable. Indeed Ghirri admits as much at column 3, stating:

> Although solid oral dosage forms are desirable, their provision is not always possible. In the case of polypeptides such as calcitonins the provision of solid oral dosage formulations is hindered by the high instability of the polypeptides. These materials are not suitable for processing into a solid dosage forms because they cannot withstand the physical and chemical stresses of conventional formulating techniques. There is therefore a need for calcitonin in a solid dosage form, more particularly there is a need for a solid oral dosage form of calcitonin. There is a further need for calcitonin in a solid dosage form with an improved shelf life, more preferably one which will not have to be stored at low temperatures.

Moreover, oral delivery of peptides faces additional hurdles not mentioned in Ghirri, i.e., circumventing the natural degradation and digestion of proteins in the gut of an intended patient, and poor bioavailability and absorption. Simply put, oral delivery of polypeptides is extremely difficult and therefore the expectation of success is quite low.

Second, neither Ghirri nor Bay provide any evidence that salmon calcitonin may be successfully used to treat osteoarthritis or to inhibit resorption and/or normalize turnover of subchondral bone in a human having osteoarthritis or osteoporosis, or in a postmenopausal woman.

Ghirri merely states:

> Calcitonins are hypocalcemic hormones found in the thyroid, parathyroid and thymus glands of man and in separate organs called ultimobranchial bodies in non-mammalian vertebrates. During hypercalcemia calcitonins reduce elevated plasma calcium concentration to normal levels by inhibiting bone resorption. Calcitonins are therefore used to treat a variety of conditions such as Paget's disease, post menopausal osteoporosis and also to treat hypocalcemia resulting from vitamin D intoxication, neoplastic disease, thyrotoxicosis or hyperthyroidism.

(Column 2). However, Ghirri provides no data to substantiate this assertion. That is, while Ghirri prepares certain oral calcitonin formulations, Ghirri provides no evidence that these formulations (or any other calcitonin formulation) could be used to treat osteoarthritis or inhibit resorption and/or normalize turnover of subchondral bone in a human having osteoarthritis or osteoporosis, or in a postmenopausal woman. In fact, Ghirri does not even administer a single composition to an animal or test a single composition in any *in vitro* model. Thus, Ghirri provides NO evidence that one may use salmon calcitonin to treat osteoarthritis or inhibit resorption and/or normalize turnover of subchondral bone in a human having osteoarthritis or osteoporosis, or in a postmenopausal woman.

This deficiency in the Office's primary reference is not supplemented by the disclosure of Bay. While Bay formulates salmon calcitonin with, e.g., 5-CNAC, and delivers this composition to rats and monkeys, Bay provides NO evidence that these compositions (or any other salmon calcitonin composition) would result in what Applicants claim, i.e., treating osteoarthritis or inhibiting resorption and/or normalizing turnover of subchondral bone in a human having osteoarthritis or osteoporosis, or in a postmenopausal woman. That is, Bay's successful delivery of salmon calcitonin to a rat or a monkey tells nothing about whether that delivery (and dose) actually results in treatment of the rat or monkey, and certainly tells nothing about whether salmon calcitonin would actually result in treatment of a human.

The present application demonstrates for the first time that calcitonin: 1) can be successfully delivered orally to humans; and 2) is efficacious in the treatment of osteoarthritis in humans (as measured by suitable biomarkers of cartilage degradation). The present application discloses that oral delivery of salmon calcitonin is superior for suppression of cartilage degradation in humans and thereby superior for treatment and prevention of osteoarthritis. In contrast, the cited references do not demonstrate that a combination of, e.g., 5-CNAC and salmon calcitonin is effective in treating osteoarthritis in humans (or preserving or stimulating cartilage etc.).

The present specification states on page 1 that, at the time of filing the instant application, no study had shown calcitonin to be effective in treating osteoarthritis in humans. Indeed, the specification makes clear on page 1 that conflicting reports existed at the time of filing as to whether calcitonin could even be used to prevent cartilage destruction. Moreover, it is known to be difficult to translate a drug-induced structural effect (like cartilage erosion) in an animal model of osteoarthrits into an expectation for efficacy in human osteoarthritis. For example, Manicourt et al., 1999 (courtesy copy submitted herewith) shows that daily subcutaneous injections of salmon calcitonin in 2-4 years old mongrel dogs with anterior cruciate ligament transection (ACLT) caused a significant reduction in the grade and size of cartilage erosion compared to placebo. However, Hayami et al., 2004 (courtesy copy submitted herewith) shows that bisphosphonates significantly and dose-dependently reduced the Mankin score in a rodent ACLT model, whereas subsequent bisphosphonate clinical studies in humans failed to demonstrate any beneficial effects on clinically relevant osteoarthritis endpoints (Bingham et al., 2006 (courtesy copy submitted herewith)). In addition, a recent phase III clinical study of the MMP-inhibitor PG-116800 failed to demonstrate any beneficial effects in patients with knee osteoarthritis. Indeed, as of this date, more than 20 anti-rheumatic MMP-inhibitor drug development programs have been discontinued; thus, positive preclinical indications (e.g., animal models) have failed over a broad range of compounds to translate into human efficacy in joint disease. Negative outcomes of human OA trials with bisphosphonates, MMP-inhibitors and others have taught the unpredictable nature of attempting to extrapolate animal models to the actual treatment of human osteoarthritis.

Prior to Applicants priority date, one does not find disclosures that suggest that use of salmon calcitonin would have a reasonable expectation of success for the treatment of patients with osteoarthritis. This unpredictability regarding the use of calcitonin to treat osteoarthritis in any animal (including humans), coupled with the unpredictability inherent in attempting to orally deliver any protein, and the unpredictable bioavailability of orally administered calcitonin in a human (as well as the required calcitonin peak serum concentrations and dosage required to achieve this) firmly indicate that at the time of filing the instant application, there was no reasonable expectation of success in achieving Applicants' claimed methods.

In sum, there is absolutely nothing in Ghirri or Bay, separately or in combination, suggesting that: 1) salmon calcitonin can be used to effectively treat osteoarthritis in a human; and 2) upon oral delivery of between 0.4 and 2.5 mg of salmon calcitonin in free or salt form formulated with 5-CNAC, SNAD, SNAC or disodium salts thereof, one can achieve therapeutic levels of salmon calcitonin in a human.[1] The combination of Ghirri and Bay provide no evidence

[1] To be applicable as prior art, the combination of applied references must provide an enabling disclosure of the desired subject matter; mere naming or description of the subject matter is insufficient, if it cannot be produced without undue experimentation. *Elan Pharm., Inc. v. Mayo Found. for Med. Educ. &*

(less so a reasonable expectation) that such highly desirable results may be obtained by using between 0.4 and 2.5 mg of salmon calcitonin in free or salt form formulated with 5-CNAC, SNAD, SNAC or disodium salts thereof. Accordingly, Applicants assert that even if, *arguendo*, the Office could maintain that one would be motivated to combine Ghirri and Bay, this combination does not render obvious Applicants' instant claims, because there is no reasonable expectation of success at achieving Applicants currently claimed methods.

III. Summary

Based on the evidence as a whole, the combination of Ghirri and Bay does not support a finding of *prima facie* obvious. *See* MPEP § 2144.08; *In re Bell*, 991 F.2d 781,784 (Fed. Cir. 1993); *In re Kulling*, 897 F.2d 1147, 1149 (Fed. Cir. 1990)). The Office has not shown where all the elements of Applicants' pending claims may be found in the combination of the cited references, nor has the Office shown a reasonable expectation of success at achieving Applicants' claimed subject matter.[2] In the present application, the results of the factual inquiries under Graham do not support that the pending claims are *prima facie* obvious under 35 U.S.C. §103(a). Accordingly, Applicants respectfully request withdrawal of the obviousness-based rejection of the pending claims.

Double Patenting

Pending claim 2 remains provisionally rejected on the ground of nonstatutory obviousness-type double patenting as allegedly unpatentable over claims 1, 9 and 10 of copending Application No. 11/577,127.

Pending claims 1-2 and 10 remain provisionally rejected on the ground of nonstatutory obviousness-type double patenting as allegedly unpatentable over claims 13-15 of copending Application No. 12/132,642.

Research, 346 F.3d 1051, 1054, 68 USPQ2d 1373, 1376 (Fed. Cir. 2003). An enabling disclosure requires the public to be in possession of a claimed invention before the date of invention. Such possession is effected if the reference teachings could have been combined with the knowledge of one of ordinary skill in the art, to make the claimed invention. *In re Donohue*, 766 F.2d 531, 226 USPQ 619 (Fed. Cir. 1985). To constitute a publication, an invention must be described sufficiently to impart to a person with ordinary skill and knowledge of the prior art the information needed to devise the invention without further genuine inspiration or undue experimentation. *Regents of U. Cal v. Howmedica, Inc.*, 210 USPQ 727, 738 (DNJ 1981); see also *Beckman Instruments, Inc. v. LKB Produkter AB*, 892 F.2d 1547, 1551 (Fed. Cir. 1989) (stating "[i]n order to render a claimed apparatus or method obvious, the prior art must enable one skilled in the art to make and use the apparatus or method."); *Motorola, Inc. v. Interdigital Tech. Corp.*, 121 F.3d 1461, 1471 (Fed. Cir. 1997); *In re Payne*, 606 F.2d 303, 314 (CCPA 1979). As discussed above, the combined teachings of Ghirri and Bay do not meet the standard of an enabling disclosure.

[2] Applicants also do not concede that there is sufficient motivation to combine Ghirri and Bay. However, it is not necessary for Applicants to detail those arguments at this time, given that the Office has not established the other *Graham* factors (i.e., reasonable expectation of success and all elements).

Pending claims 1-2 remain provisionally rejected on the ground of nonstatutory obviousness-type double patenting as allegedly unpatentable over claims 26, 28 and 29 of copending Application No. 12/093,383.

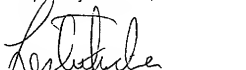
The present application is further along in prosecution than the above-identified co-pending applications. Applicants therefore respectfully request that upon allowance of the claims under consideration in this application, the Examiner withdraw the double patenting rejection in this application, and make a provisional double patenting rejection in the above-identified co-pending applications. The provisional rejection in the above-identified co-pending applications may then be converted into a double patenting rejection upon the present application issuing into a patent. See MPEP 804.

CONCLUSION

In light of the above amendments, observations and remarks, Applicants respectfully submit that the presently claimed invention satisfies 35 U.S.C. §112, and is neither disclosed nor suggested by any art of record. Accordingly, reconsideration and allowance of all claims in this application is earnestly solicited.

Applicants' undersigned attorney may be reached in our New Jersey office by telephone at (862) 778-9308. All correspondence should continue to be directed to our below-listed address.

Respectfully submitted,



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